IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Erion *et al.*	
Serial No.: 09/978,454	Group Art Unit: 1616
Filed: October 15, 2001	Examiner: Dameron Jones
Title: NOVEL PRODRUGS FOR PHOSPHORUS-CONTAINING COMPOUNDS	

Mail Stop Amendment
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MARK D. ERION
PURSUANT TO 37 C.F.R. § 1.132

I, Mark D. Erion, a citizen of the United States, declare and say that:

1. I have a Ph.D. in synthetic organic chemistry from Cornell University, and I have over 16 years experience in the pharmaceutical industry. I am currently the Executive Vice President of Research & Development at Metabasis Therapeutics, Inc. in San Diego, CA. As such, I am responsible for all discovery research and development. I am an inventor of the HepDirect™ prodrug technology, a platform technology useful for targeting drugs to the liver. I also headed the R&D team responsible for the identification of clinical candidates for diabetes, hepatitis B, and hepatocellular carcinoma. Prior to co-founding Metabasis Therapeutics in 1997, I was the Division Vice President of Research at Gensia, Inc. in San Diego, CA. Prior to joining Gensia in 1991, I was a group leader at Ciba-Geigy where I directed a team in the area of protein engineering at Ciba-Geigy's Central Research Laboratories in

CERTIFICATE OF MAILING
(37 C.F.R. §1.8)

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage via Express Mail, Label No. ER201538729 US, in an Express Mail envelope addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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October 14, 2004
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Switzerland. I have over 80 publications and 25 U.S. patents. Through my work, I have had extensive experience in the area of prodrugs, including the invention of the HepDirect™ prodrug technology.

2. I am an inventor of the above-referenced application for the patent filed on October 15, 2001. I have reviewed the pending claims in this case, the specification, and the Office Action mailed April 14, 2004.

3. It is my understanding from the Office Action that the Examiner finds claims 168-185 to be indefinite and lacking written description, because of the use of the term "M is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via a carbon, oxygen, or nitrogen atom, with the proviso that $M\text{-}PO_3^{2-}$ is not an FBPase inhibitor." In particular, it is my understanding that the Examiner believes that a person of ordinary skill in the art would not understand what is claimed, because there are no structures for M in the claim and because it is unclear what is meant by "$M\text{-}PO_3^{2-}$ is not an FBPase inhibitor."

4. Contrary to the Examiner's position, a person of ordinary skill in the art can understand what is claimed and what is excluded.

5. First, a person of ordinary skill in the art would understand what drugs are biologically active when attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4}$.

6. The specification defines the term "biologically active drug or agent" as

> refers to the chemical entity that produces a biological effect. In this invention, biologically active agents refers to $M\text{-}PO_3^{2-}$, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$ where M can be the same M as in the parent drug or metabolite. (p. 21, lines 8-10)

7. The specification also explains that "The present invention is directed towards novel prodrugs of phosphate, phosphonate, and phosphoramidate compounds which in their active form have a phosphate, phosphonate, or phosphoramidate group." (p. 1, lines 10-12) "The invention is directed to the use of new cyclic phosph(on)ate ester methodology which allows compounds to be efficiently converted to phosph(on)ate containing compounds by p450 enzymes found in large amounts in the liver and other tissues containing these specific enzymes." (p. 22, lines 37-40) "This methodology can be applied to various drugs and to diagnostic imaging agents." (p. 22, line 40) Moreover, "The Background of the Invention" discusses numerous examples where the phosphates, etc. are biologically active. For example, the specification specifically discusses 3TC and araA:

> A large class of drugs known to be active against hepatitis are generally nucleoside or nucleotide analogs that are phosphorylated inside cells to produce the biologically active triphosphate. Examples include Lamivudine (3TC) and Vidarabine (araA). p. 5, lines 16-18

The specification also defines the term "parent drug" and gives an example of how AZT-triphosphate is biologically active:

> The term "parent drug" refers to MH for phosph(oramid)ates where M is connected to –P(O)(OR)(OR) via oxygen, sulfur, or nitrogen, and M-PO_3^{2-} when M is connected to –P(O)(OR)(OR) via carbon. For example, AZT can be thought of as a parent drug in the form of MH. In the body AZT is first phosphorylated to AZT-PO_3^{2-} and then further phosphorylated to form AZT-triphosphate, which is the biologically active form. The parent drug form MH only applies when M is attached via N, S or O. In the case of PMEA, the parent drug form is M-PO_3^{2-}.
> (specification p. 21, lines 1-7)

From the specification descriptions and the examples regarding 3TC, araA, and AZT, one of ordinary skill in the art is aware that the biologically active form of the compound is interacting with the receptor or enzymes such as viral or animal polymerases, for example.

8. Additionally, the Applicants made numerous prodrugs of this invention. (*see* Specification pp. 132-161) Additionally, Applicants have conducted numerous tests on compounds of this invention including: activation by rat and human liver microsomes (Exs. D and E); activation by recombinant CYP3A4 (Ex. G); and inhibition of glucose production in rat hepatocytes (Ex. J).

9. A person of ordinary skill in the art reviewing this specification can apply this technology to any M that is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo*. Applying the invention generally does not depend on the structure of M.

10. Given the guidance in the specification and what was known in the art as of March 1998, a person of ordinary skill in the art would have understood the claim language and been able to determine what was included within the scope of the claims.

11. Second, the determination of what is or what is not an FBPase inhibitor is a matter of routine screening and was a matter of routine screening by March of 1998. A person of ordinary skill in the art would be guided by the specification. The Applicants note the following quotes from the specification explaining what FBPase inhibitors are and how to test for FBPase activity:

> "The phosphate and phosphonate compounds may be inhibitors of FBPase activity, preferably with IC50s of about 10 μM on the human liver enzyme..." (p. 47, lines 15-16)
>
> "Moreover, when the parent drug is an FBPase inhibitor, the production of the drug is supported by the ability of the prodrug to result in potent gluconeogenesis inhibition (Example J)." (p. 30, lines 20-22)
>
> "Esters disclosed in the invention are converted to the parent phosph(on)ate in cells and tissues, especially hepatocytes and liver, as indicated by measurement of the intracellular drug metabolites in hepatocytes using the procedure described in Example I and by the

inhibition of glucose production by rat hepatocytes when M-PO_3^{2-} is an FBPase inhbitor (Example J)." (p. 48, lines 18-20)

12. It is a matter of routine testing to determine whether or not a given compound is an FBPase inhibitor. For example, enzymatic activity is easily determined spectrophotometrically. By March of 1998 such a spectrophotometric analysis was easily and routinely accomplished. In addition, by March of 1998, High Throughput Screening allowed a rapid evaluation of large numbers of compounds. (1000s per day). The routine nature of High Throughput Screening is evidenced by many pre-March 1998 articles including Burbaum and Sigal, New Technologies for High-Throughput Screening, *Curr. Opin. Chem. Biol.* **1997**, 1:72-78; Wu *et al.*, A High-Throughput STAT Binding Assay Using Fluorescence Polarization, *Anal. Biochem.* **1997, 249**:29-36; Dhundale and Goddard, Reporter Assays in the High Throughput Screening Laboratory: A Rapid Robust First Look?, *J. of Biomolecular Screening* **1996, 1**:115-118; and Cook, Scintillation Proximity Assay: A Versatile High-Throughput Screening Technology, *Drug Discovery Today* **1996, 1**:287-294.

13. Given the guidance in the specification and the routine nature of the testing involved, as of March 1998, a person of ordinary skill in the art can easily determine what compounds of formula M-PO_3^{2-} are not FBPase inhibitors and thus are excluded from the scope of the claims.

14. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

10/14/04
Date

Mark D. Erion, Ph.D.